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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,017	02/13/2002	Thomas E. Jenkins	P-009-RC2	8903
27038	590 06/14/2005		EXAMINER	
THERAVANCE, INC.			SHIBUYA, MARK LANCE	
901 GATEWAY BOULEVARD SOUTH SAN FRANCISCO, CA 94080			ART UNIT	PAPER NUMBER
			1639	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

•	Application No.	Applicant(s)			
	10/075,017	JENKINS ET AL.			
Office Action Summary	Examiner	Art Unit			
	Mark L. Shibuya	1639			
The MAILING DATE of this communication appears on the cover sheet with the correspondence address Period for Reply					
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION. - Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely. - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).					
Status					
1) Responsive to communication(s) filed on 20 Ja	nuary 2005.				
2a) ☐ This action is FINAL . 2b) ☒ This	action is non-final.				
	Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11, 453 O.G. 213.				
Disposition of Claims					
4) Claim(s) 64-70 is/are pending in the application. 4a) Of the above claim(s) is/are withdrawn from consideration. 5) Claim(s) is/are allowed. 6) Claim(s) 64-70 is/are rejected. 7) Claim(s) is/are objected to. 8) Claim(s) are subject to restriction and/or election requirement.					
Application Papers					
9)☐ The specification is objected to by the Examiner.					
10)☐ The drawing(s) filed on is/are: a)☐ accepted or b)☐ objected to by the Examiner.					
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).					
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d). 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.					
Priority under 35 U.S.C. § 119					
12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of: 1. Certified copies of the priority documents have been received. 2. Certified copies of the priority documents have been received in Application No 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received.					
Attachment(s) 1) Notice of References Cited (PTO-892) 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date	4) Interview Summary Paper No(s)/Mail Da 5) Notice of Informal P 6) Other:				

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DETAILED ACTION

1. Claims 64-70 are pending and examined.

Election/Restrictions

2. The requirement for election/restriction and applicant's election, as set forth in the prior Office action, is withdrawn. Applicant's request for reconsideration of the restriction requirement is acknowledged. Applicant's election of the Group where the linker is –C(O)-alkylene-alkylene-C(O)-, is taken as an election of species, because of the substantial search and administrative burden. However, the other species remain withdrawn from consideration, there being no allowable generic or linking claim.

Priority

Acknowledgement is made of applicant's claim that this application, filed 2/13/2002, is a continuation of U.S. Serial No. 09/499,176, filed on 2/7/2000, abandoned on 5/24/02; which is a continuation of U.S. Serial No. 09/327,096, filed on 6/7/1999, abandoned on 2/8/2000; which application claims the benefit of U.S. Provisional Application Serial No. 60/088,465, filed 6/8/1998, and U.S. Provisional Application Serial No. 60/093,068, filed 716/1998.

Withdrawn Claim Objections - 35 USC § 112

4. The objection to the claims is withdrawn.

Withdrawn Claim Rejections - 35 USC § 112

5. The rejection of claims 64-68 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendments to the claims, entered 1/20/2005.

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6. The rejection of claims 64-68 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for ligands taught by the instant specification, does not reasonably provide enablement for all ligands that bind to a cell membrane transporter or to any cell membrane transporter that are ion channels or to any sodium ion channel, is withdrawn in view of applicant's arguments, entered 1/20/2005.

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7. Applicant's arguments, see Reply at p. 9, para 2, filed 1/20/2005, with respect to the rejection(s)of claim(s) 64-68 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of newly found prior art references, as set forth below in new rejections under 35 U.S.C. 103(a).

Maintained Claim Rejections - 35 USC § 112

8. Claims 64-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a *Written Description Rejection*. This rejection maintains the reasons of record as set forth in previous Office action, mailed 09/30/2004, and is further extended to new claims 69 and 70, and expanded upon as follows.

The specification as filed does not permit the skilled artisan to envision the claimed methods for preparing libraries of ligand compounds, having the detailed chemical structure of the encompassed genera of all divalent ligand compounds that bind to a cell membrane transporter or to cell membrane transporters that are ion channels or sodium ion channels, and where the functional group of each ligand in a divalent ligand compound of the prepared library has functionalized at different positions

relative to the other functionalized ligands and linked together at those positions. The claims are not drawn to structures for the ligands or linkers for preparing the libraries, except in broad terms encompassing genera of organic groups.

Response to Arguments

Applicant argues that to practice the claimed invention the practitioner merely selects a ligand as a starting material from, for example, the published literature. Applicant argues that the Specification, particularly Table 1 on pages 214-215 and Table 6 on pages 221-225, "give hundreds, if not thousands, of specific examples of known ligands for at least 15 different types of cell membrane transporters." Applicant states that "[g]iven the extensive disclosure in Applicants' specification of many hundreds of suitable ligands for many types of cell membrane transporters, one skill in the art would clearly recognize that the inventors had possession of the claimed method at the time the application was filed."

Applicant's arguments filed 1/20/2005 have been fully considered but they are not persuasive. The claims are drawn to a method of preparing a library of compounds of the formula L—X—L, where L is a ligand and X is a linker, and in addition to selecting a ligand that binds to a cell membrane transporter, the ligands must be functionalized at different sites, so that a linker reacting with the different functional groups will provide a library of ligand compounds, where the ligands are linked at different sites. The specification discloses many examples of ligands, however, the specification does not exemplify a library of ligand compounds of the formula L—X—L, where the functional group of each functionalized ligand is located at different positions relative to the other

functionalized ligands. The specification's disclosure of hundreds of ligands does not extend to libraries of divalent ligand compounds, where the ligands that have been functionalized at different points on the ligands and linked at those different points. As the applicant states, the disclosure provides many ligands as starting material; however, the specification does not disclose preparing a representative number of libraries by starting with the listed unmodified ligands and functionalizing them at different points, and then linking the ligands at the different points. The specification does not provide a representative number of ligand compounds where the ligands have been functionalized at different points or positions, or the linkers that connect them. Therefore, one of skill in the art would not recognize that the inventors had possession of the claimed invention.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 64-67, 69 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Portoghese**, (J. Med. Chem., 35 (11): 1927-1937 (1994); IDS filed 4/30/2002, ref. no. C11), **Breslow et al.**, J. Am. Chem. Soc. March 28, 1998, Vol. 120, pp. 3536-3537, and **Joslyn et al.**, (J. Med. Chem., 31: 1489-1492 (1988); IDS filed 4/30/2002, ref. no. C7).

Claims 64-67, 69 and 70 are drawn to a method of preparing a library of compounds of the formula: L-X-L, wherein each L is independently a ligand which binds to a cell membrane transporter, wherein X is a linker of the formula -C(O)-alkylene-alkylene-C(O)-; the method comprising the steps of: (a) identifying a ligand compound which binds to a cell membrane transporter; (b) providing a plurality of functionalized ligands, wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assaying each compound of the library to determine the affinity of each compound for the cell membrane transporter; wherein the linker has a chain length between reactive functional groups of from about 2 Å to 100 Å; and wherein the cell membrane is an ion channel (as in claim 67).

Portoghese, (J. Med. Chem., 35 (11): 1927-1937 (1994); IDS filed 4/30/2002, ref. no. C11), at p. 1932, para 4 – p. 1935, para 2, particularly Fig. 6 and p. 1933, para 1, teaches methods of preparing a library of bivalent compounds of the formula: L-X-L, wherein each ligand is a naltrexone-derived pharmacophore that binds to an opioid

receptor, wherein X is a spacer that is a linker of the formula –C(O)-R-C(O)-, wherein R is CH₂CH₂ or CH=CH; the method comprising the steps of: (a) identifying a ligand compound which binds to an opioid receptor; (b) providing a plurality of functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assay each compound of the library to determine the affinity of each compound for the opioid receptor; and absent evidence to the contrary, wherein the linker has a chain length between reactive functional groups of from about 2 Å to 100 Å.

Portoghese does not teach ligand compounds where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, and that bind cellular membrane transporters; and wherein the cell membrane is an ion channel.

Breslow et al., J. Am. Chem. Soc. March 28, 1998, Vol. 120, pp. 3536-3537, throughout the publication, teach methods of making a plurality of different cyclodextrin dimer compounds, reading on a library of said compounds, and where the cyclodextrins of the compounds are linked at different relative positions.

Joslyn et al., (J. Med. Chem., 31: 1489-1492 (1988); IDS filed 4/30/2002, ref. no. C7), at the abstract and p. 1489, para 1 – p. 1491, para 2, teach methods of preparing a library of divalent compounds of the formula: L-X-L, wherein each ligand is a dihydropyridine that binds to a cell membrane transporter that is a calcium ion channel; the method comprising the steps of: (a) identifying a dihydropyridine ligand; (b) providing a plurality of functionalized ligands; (c) providing a linker comprising two

reactive functional groups; (d) reacting the linker with the dihydropyridine to provide the library of compounds; further comprising assay each compound of the library to determine the affinity of each compound for the cell membrane transporter.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have combined methods for producing libraries of divalent ligand compounds comprising a linker of the formula –C(O)-alkylene-alkylene-C(O)-, (as taught by the reference of Portoghese), with methods for producing ligand compound libraries where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, as taught by Breslow, and with methods of producing libraries of divalent ligand compounds that target cellular membrane transporters, (as taught by reference of Joslyn).

One of ordinary skill in the art would have been motivated to produce libraries of divalent ligand compounds comprising a linker of the formula -C(O)-alkylene-alkylene-C(O)-, where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, wherein libraries of divalent ligand compounds target cellular membrane transporters, because Portoghese (bridging paragraph pp. 1932-33) teaches the use of this linker as a spacer that permits varying spacer length, facilitates elaboration through standard peptide chemistry, avoids incremental increases in the hydrophobic properties upon lengthening, and introduces symmetry so as to connect as divalent ligands of calcium ion channel antagonists; because Breslow teaches that linking different points on the ligands permits identifying ligand compounds that bind more strongly to a target than other members of the library,

and because Joslyn (p. 1489) teaches that ligands are of proven value in treating cardiovascular disease and divalent ligands may enhance affinity by a minimum of twofold. One of ordinary skill in the art would have had a reasonable expectation of success in preparing the library as claimed, because ligands targeting membrane transporters, linkers and methods for functionalizing the ligands for linkage, were known in the art.

10. Claims 64-67, 69 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Portoghese**, (J. Med. Chem., 35 (11): 1927-1937 (1994); IDS filed 4/30/2002, ref. no. C11), **Joseph-McCarthy et al.**, Proteins: Structure, Function, and Genetics 29:32-58 (1997), and **Joslyn et al.**, (J. Med. Chem., 31: 1489-1492 (1988); IDS filed 4/30/2002, ref. no. C7).

Claims 64-67, 69 and 70 are drawn to a method of preparing a library of compounds of the formula: L-X-L, wherein each L is independently a ligand which binds to a cell membrane transporter, wherein X is a linker of the formula -C(O)-alkylene-alkylene-C(O)-; the method comprising the steps of: (a) identifying a ligand compound which binds to a cell membrane transporter; (b) providing a plurality of functionalized ligands, wherein the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assaying each compound of the library to determine the affinity of each compound for the cell

membrane transporter; wherein the linker has a chain length between reactive functional groups of from about 2 Å to 100 Å; and wherein the cell membrane is an ion channel (as in claim 67).

Portoghese, (J. Med. Chem., 35 (11): 1927-1937 (1994); IDS filed 4/30/2002, ref. no. C11), at p. 1932, para 4 – p. 1935, para 2, particularly Fig. 6 and p. 1933, para 1, teaches methods of preparing a library of bivalent compounds of the formula: L-X-L, wherein each ligand is a naltrexone-derived pharmacophore that binds to an opioid receptor, wherein X is a spacer that is a linker of the formula –C(O)-R-C(O)-, wherein R is CH₂CH₂ or CH=CH; the method comprising the steps of: (a) identifying a ligand compound which binds to an opioid receptor; (b) providing a plurality of functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the functionalized ligands to provide the library of compounds; further comprising assay each compound of the library to determine the affinity of each compound for the opioid receptor; and absent evidence to the contrary, wherein the linker has a chain length between reactive functional groups of from about 2 Å to 100 Å.

Portoghese does not teach ligand compounds where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, and that bind cellular membrane transporters; and wherein the cell membrane is an ion channel.

Joseph-McCarthy et al., Proteins: Structure, Function, and Genetics 29:32-58 (1997), throughout the publication and abstract, and at p. 33, para 2-p. 34, para 1, p. 37, para 3-p. 38, para 1, p. 39, para 3-p. 40, para 1, Figure 5, p. 48 para 2-p. 51, para 1,

Figures 11 and 12 teach designing by aid of computer (determining energy minima based on the known structure of the target poliovirus capsid) and making trivalent ligands targeting the capsid, wherein the connection of links to indole rings is varied between alternative ligands.

Joslyn et al., (J. Med. Chem., 31: 1489-1492 (1988); IDS filed 4/30/2002, ref. no. C7), at the abstract and p. 1489, para 1 – p. 1491, para 2, teach methods of preparing a library of divalent compounds of the formula: L-X-L, wherein each ligand is a dihydropyridine that binds to a cell membrane transporter that is a calcium ion channel; the method comprising the steps of: (a) identifying a dihydropyridine ligand; (b) providing a plurality of functionalized ligands; (c) providing a linker comprising two reactive functional groups; (d) reacting the linker with the dihydropyridine to provide the library of compounds; further comprising assay each compound of the library to determine the affinity of each compound for the cell membrane transporter.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have combined methods for producing libraries of divalent ligand compounds comprising a linker of the formula –C(O)-alkylene-alkylene-C(O)-, (as taught by the reference of Portoghese), with methods for producing ligand compound libraries where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, as taught by Joseph-McCarthy, and methods of producing libraries of divalent ligand compounds that target cellular membrane transporters, (as taught by reference of Joslyn).

One of ordinary skill in the art would have been motivated to produce libraries of divalent ligand compounds comprising a linker of the formula –C(O)-alkylene-alkylene-C(O)-, where the functional group of each functionalized ligand is located at different positions relative to the other functionalized ligands, wherein libraries of divalent ligand compounds target cellular membrane transporters, because Portoghese (bridging paragraph pp. 1932-33) teaches the use of this linker as a spacer that permits varying spacer length, facilitates elaboration through standard peptide chemistry, avoids incremental increases in the hydrophobic properties upon lengthening, and introduces symmetry so as to connect as divalent ligands of calcium ion channel antagonists; because Joseph-McCarthy teaches that linking different points on the ligands result in different ligand compounds that may bind better than other members of the library, and because Joslyn (p. 1489) teaches that ligands are of proven value in treating cardiovascular disease and divalent ligands may enhance affinity by a minimum of twofold. One of ordinary skill in the art would have had a reasonable expectation of success in preparing the library as claimed, because ligands targeting membrane transporters, linkers and methods for functionalizing the ligands for linkage, were known in the art.

11. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over

Portoghese, (J. Med. Chem., 35 (11): 1927-1937 (1994); IDS filed 4/30/2002, ref. no.

C11), Breslow et al., J. Am. Chem. Soc. March 28, 1998, Vol. 120, pp. 3536-3537, and

Joslyn et al., (J. Med. Chem., 31: 1489-1492 (1988); IDS filed 4/30/2002, ref. no. C7),

as applied to claims 64-67, 69 and 70 above, and further in view of **Ackerman et al.**, (New England Journal of Medicine, 336(22): 1575-1586 (1997); IDS filed 4/30/2002, ref. no. C1).

Portoghese, (J. Med. Chem., 35 (11): 1927-1937 (1994); IDS filed 4/30/2002, ref. no. C11), at p. 1932, para 4 – p. 1935, para 2, particularly Fig. 6 and p. 1933, para 1, teaches methods of preparing a library of bivalent compounds of the formula: L-X-L, as relied upon in the above rejection.

Breslow et al., J. Am. Chem. Soc. March 28, 1998, Vol. 120, pp. 3536-3537, is relied upon as in the rejection above.

Joslyn et al., (J. Med. Chem., 31: 1489-1492 (1988); IDS filed 4/30/2002, ref. no. C7), is relied upon as in the above rejection.

Portoghese, Breslow et al., and Joslyn et al. do not teach methods for preparing ligand compound libraries, wherein the cell membrane transporter is a sodium ion channel.

Ackerman et al., (New England Journal of Medicine, 336(22): 1575-1586 (1997); IDS filed 4/30/2002, ref. no. C1) at p. 1576, Table 1, p. 1584, table 2, teach drugs that are ligands that bind to cellular sodium ion channel membrane transporters.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have combined methods for producing libraries of divalent ligand compounds as above, and wherein the ligands target sodium ion channel.

One of ordinary skill in the art would have been motivated to use ligands in methods to prepare ligand compound libraries that target sodium ion channel because the reference of Ackerman teaches drugs, including anticonvulsant and antiarrhythmic drugs, that are ligands which target the sodium ion channels. One of ordinary skill in the art would have had a reasonable expectation of success in making libraries comprising ligands that target sodium ion channels, because such ligands were known in the art.

12. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Portoghese, (J. Med. Chem., 35 (11): 1927-1937 (1994); IDS filed 4/30/2002, ref. no. C11), Joseph-McCarthy et al., Proteins: Structure, Function, and Genetics 29:32-58 (1997), and Joslyn et al., (J. Med. Chem., 31: 1489-1492 (1988); IDS filed 4/30/2002, ref. no. C7), as applied to claims 64-67, 69 and 70 above, and further in view of Ackerman et al., (New England Journal of Medicine, 336(22): 1575-1586 (1997); IDS filed 4/30/2002, ref. no. C1).

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It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have combined methods for producing libraries of divalent ligand compounds as above, and wherein the ligands target sodium ion channel.

One of ordinary skill in the art would have been motivated to use ligands in methods to prepare ligand compound libraries that target sodium ion channel because the reference of Ackerman teaches drugs, including anticonvulsant and antiarrhythmic drugs, that are ligands which target the sodium ion channels. One of ordinary skill in the art would have had a reasonable expectation of success in making libraries comprising ligands that target sodium ion channels, because such ligands were known in the art.

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Conclusion

13. Claims 64-68 are rejected.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya

Examiner Art Unit 1639

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